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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,965	11/13/2001	Pierre Colas	EGYP 3.0-015	4646

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/066,965	COLAS ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-65,67,70-78 and 84-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65, 67, 70-71, 74, 77-78 , 84- 88 and 90* is/are rejected.

7)☒ Claim(s) *72,73,75,76,88 and 89* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.

2. Applicant's response to the Office Action mailed May 17, 2006 on November 20, 2006 is acknowledged.

Claim Disposition

3. Claims 63-65, 67, 70-78 and 84-92 are pending and are under examination.

Maintained and Amended-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 63-65, 67, 70-71, 74, 77-78 , 84- 88 and 90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention encompasses a large variable genus of proteins. The claims encompass a peptide aptamer (intracellular recognition molecule,) and any target bound to any TRX-like protein as a platform interacting with an unspecified amount of targets (see claim 63 for example); and the claims encompass any intracellular recognition molecules and any target bound to any platform having the capacity to interact with the unspecified amount of targets. The claims are drawn also to any peptide having 5 to 60 amino acids. Note that the word "having" is open thus said peptide is limitless. The specification discloses that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9). However, the only intracellular recognition molecules exemplified are peptide aptamers, for example Cdk2 (see page 12, for example). The platform preferred is thioredoxin, however, the claims are also directed to thioredoxin-like proteins (see claim 63 and page 12 of the specification), however, none is disclosed. It is noted also that paragraph 0059 of the specification disclose that the "thioredoxin-like proteins have at least 18%, preferably at least 40% and most preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over 80 amino acids", which includes an enormous amount of variability, consequently, the desired effect of bonding of the recognition molecule R to the platform may not occur. The specification lacks adequate written description with regard to the variable T (target). In addition, the claims are directed to a recognition molecule that can vary in length, hence may not function as desired, knowing that structural changes can affect the

structure-function relationship of a protein. No correlation is made between structure and function.

Therefore, the skilled artisan cannot envision the detailed chemical structure of the peptide aptamer and TRX-like protein encompassed in the claims, thus the claimed invention lacks adequate written description. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the

complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

5. Claims 63-65, 67, 70-71, 74, 77-78 , 84- 88 and 90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intracellular recognition molecules that are peptide aptamer (such as the sequences disclosed on page 33 and anti-Cdk2 and others listed on page 12 of the specification as well as cited in the prior art), does not reasonably provide enablement for any intracellular recognition molecule or target or TRX-like protein (claim 63 for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in

the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass a peptide aptamer (intracellular recognition molecule,) and any target bound to any TRX-like protein as a platform interacting with an unspecified amount of targets (see claim 63 for example); any peptide that comprises 5 to 60 amino acids; and the claims encompass any intracellular recognition molecules and any target bound to any platform having the capacity to interact with the unspecified amount of targets. The specification discloses that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9). However, the only intracellular recognition molecules exemplified are peptide aptamers, for example Cdk2 (see page 12, for example). The platform preferred is thioredoxin, however, the claims are also directed to thioredoxin-like proteins (see claim 63 and page 12 of the specification), however, none is disclosed. It is noted also that paragraph 0059 of the specification disclose that the "thioredoxin-like proteins have at least 18%, preferably at least 40% and most preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over 80 amino acids", which includes an enormous amount of variability, consequently, the desired effect of bonding of the recognition molecule R to the platform may not occur. The specification lacks adequate guidance with regard to the variable T (target). In addition, the claims are directed to a recognition

molecule that can vary in length, hence may not function as desired, knowing that structural changes can affect the structure-function relationship of a protein.

Note that the intracellular recognition molecule R comprises a recognition domain which is disclosed as "comprising" (see for example claims 72, 73 and 75) or "consists" (see for example claim 64) of peptides having lengths of 10-40, mutations wherein 1-3 amino acid residues are changed or has for example, the amino acid sequence "QVWSLWALGWRWLRRYGWNM" (see claims 72-73, 75 and 64 and page 60 of the specification), which represents open and closed language in association with the structure and there is no indicia as to whether or not the structure once modified will retain the prescribed function or have biological activity. In addition, the preferred peptide is ten to forty amino acids, however, a 20-mer is exemplified. It is also disclosed on page 28 that the peptide can have a mutant having from one to five, preferably one to three amino acid changes with respect to said sequence and there is no indicia as to a conserved region or where in the sequence the modifications will occur and if said modification can be tolerated in the sequence. Due to the large quantity of experimentation necessary to generate an intracellular recognition molecule comprising a domain that is variable that can interact with any target and to screen same for activity and the lack of guidance/direction provided in the instant specification with regard to the variables in the invention, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for

example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims as the claims broadly read on intracellular recognition molecule fragments or any target or platform. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification, as the variables are described in vague terms. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct any intracellular recognition molecule with a variable domain having the capacity to specifically interact with any target.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of intracellular recognition molecules and targets, which may

or may not possess the ability to interact. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test all intracellular recognition molecules encompassed in the claims would constitute undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Response to Arguments

6. The amendment/remarks have been considered. Note also that the rejections under 35 U.S.C. 112, first paragraph written description of record has been maintained and amended for the reasons stated above and herein. Applicant's remarks state that claim 63 has been amended to incorporate the limitation of claim 69, which was not rejected, thus the rejections of record under 35 U.S.C. 112, first paragraphs are obviated (written description and enablement). This argument is not persuasive because the issues raised in the rejections pertain to the claim of a genus of proteins not adequately described or supported by the instant specification. The cancelled claim 69 recited a specific Kd value, which does not provide enablement to the claimed genus of proteins described as "TRX-like proteins" for example. Furthermore, claim 63 previous to amendments recited a Kd value and still rejected under 35 U.S.C. 112 first paragraph. The issue at hand is that the claims are drawn to a genus of peptides having a length of 5-60 amino acids for which no structure is provided, a genus of TRX-like proteins, a genus of proteinaceous recognition domains, for which no correlation is made between structure and function, thus not adequately described. The instant specification is not commensurate in scope with the claims. As stated above the claims encompass any peptide aptamer and any TRX-like protein, which is not supported by the disclosure, thus not enabled. Therefore, the rejections remain.

Conclusion

7. Claims 72-73, 75-76and 88-89 are objected to as depending from a rejected based claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Primary Examiner

2/10/07

HOPE ROBINSON
PRIMARY EXAMINER